

REMARKS

Claims 10-15, 21, and 23-25 are pending. The applicants have amended claim 13 to correct an error in the preamble.

The Office action sets forth a single rejection, which the applicants address, below.

The §103 Rejections

The Office rejected claims 10 and 12-13 under 35 U.S.C. § 103(a), arguing that the claims are obvious in view of the Burke reference (WO 0236162) when combined with the Hinton et al. reference (*N. Eng. J. Med.*, 315:485-487 (1986)). The applicants respectfully disagree that the rejection is proper.

The Burke reference discloses that one of the claimed compounds of the invention, compound II, is “able to reduce the amount of cell death among the neurons of the retina and optic nerve.” But this is unremarkable. As the applicants observe:

it has been known that certain compounds, including certain alpha adrenergic agonists such as brimonidine, are able to provide neuroprotective activity to optic or retinal cells and the nerve cells of the spine when applied topically or injected at the site of nerve damage.

Specification, at ¶ 25. What has not been known – and what the Burke reference does not suggest or disclose – is that there are alpha-2B or 2C receptors in those areas of the brain responsible for Alzheimer’s disease in any non-trivial amount:

not been thought that such agents would be effective agents for the treatment of neurodegenerative conditions of the brain, such as Alzheimer’s disease and Parkinson’s disease, since it has previously not been thought that alpha 2B and/or alpha 2C receptors were plentiful in these areas of the brain.

Id. Moreover, one of ordinary skill would not have thought that one could treat Alzheimer’s disease, or any other systemic neurodegenerative condition, with the

compounds of the invention because these compounds produce the major side effect of sedating the patient:

while alpha adrenergic receptor agonists have been shown to have useful neuroprotective activities when administered for topical treatment, the sedative effects of these compounds observed at therapeutic doses have severely limited their usefulness as a practical matter as non-topical or systemic agents.

Specification, at ¶ 25. Hence, while the Burke reference discloses that a compound of the invention is neuroprotective, there are reasons why one of ordinary skill in the art would not expect that one could successfully treat Alzheimer's disease with the compound. The Burke reference discloses only that compound II may be used to prevent cell death in the retina and optic nerve: it says nothing about the ability of the compound to prevent cell death in brain, or whether one would expect to find its target there (one would not), or whether one would want to deliver such a heavily sedating compound to the brain.

There is moreover a high degree of unpredictability in this field. That a compound is neuroprotective in the eye does not necessarily mean that it will be neuroprotective in the brain. The history of research in this field is replete with failures in translating in vitro results to clinical success. Lutsep and Clark describe this in the field of stroke research. They tell of

Neuroprotective agents . . . [which] focus on the penumbra region of the stroke, where the cells are dysfunctional due to ischemia but not yet irreversibly injured like the cells in the core of the stroke. These therapies target events in the ischemic cascade to prevent ongoing injury to the ischemic brain.

Curr. Neurol. and Neurosci. Reports, 1:13–18 (2001), at 13. So far so good, but the authors reach this stark conclusion:

No neuroprotective agent has yet been found to be clinically efficacious despite significant research effort.

Id. One should not expect, therefore, that because a compound is neuroprotective in the eye, that it would be effective in treating Alzheimer's disease – especially here, where it was not known at the time the present application was filed that alpha-2B and 2C receptors were present in the brain in sufficient number to enable one to target these receptors in the treatment of the disease.

The Hinton reference discloses merely that patients with Alzheimer's disease have axonal degeneration of the optic nerve. This, too, is unremarkable. It does not suggest that an agent that is effective a protecting the optic nerve would also be effective in treating Alzheimer's disease: to say otherwise confounds cause and effect. In advanced stages of Alzheimer's disease, for example, a patient may be incontinent. Incontinence is treated with diapers. But it does not mean that diapers would be effective in treating dementia. In the same manner, an agent that is effective at treating the optic nerve is not necessarily effective in treating dementia simply because the same disease process produced it.

For the foregoing reasons, the applicants respectfully request that the Office withdraw the § 103 rejection.

Please use Deposit Account 01-0885 for the payment of any extension of time fees under 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

/Joel B. German/

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Joel German

Registration No. 48,676
CUSTOMER NUMBER: 51957

ALLERGAN, INC.
2525 Dupont Drive
Irvine, California 92612
Telephone: 714.246.4920
Facsimile: 714.246.4249